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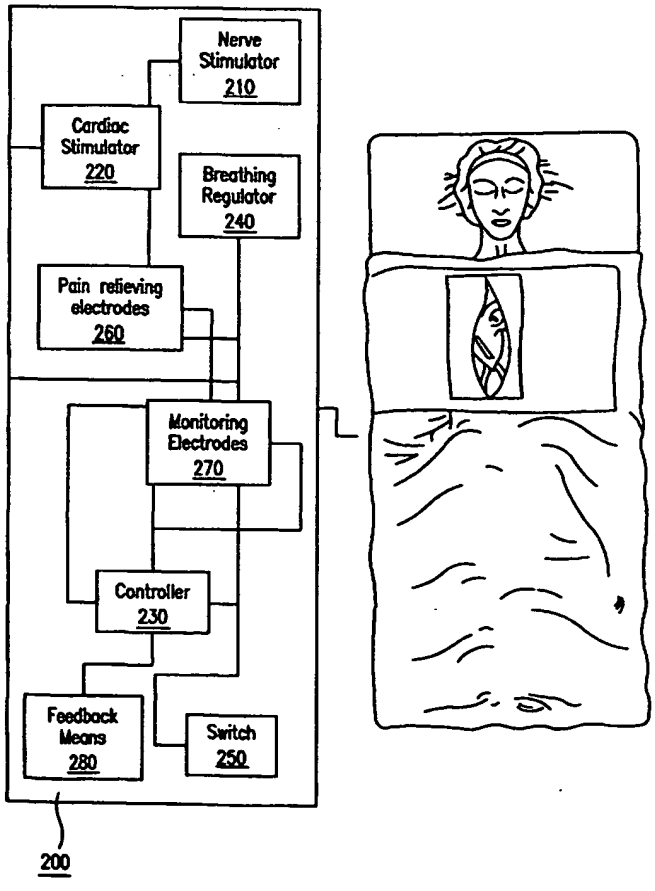

(57) Abstract: A method of performing a medical procedure, such as surgery, is provided. A nerve is stimulated in order to adjust the beating of the heart to a first condition, such as a stopped or slowed condition. The medical procedure is performed on the heart or another organ. The stimulation of the nerve is stopped in order to adjust the beating of the heart to a second condition, such as a beating condition. The heart itself may also be stimulated to a beating condition, such as by pacing. The stimulation of the nerve may be continued in order to allow the medical procedure to be continued. Systems and devices for performing the medical procedure are also provided.

WO 02/26320 A1

METHOD AND SYSTEM FOR ENDOTRACHEAL/ESOPHAGEAL STIMULATION PRIOR TO AND DURING A MEDICAL PROCEDURE

FIELD OF THE INVENTION

This invention relates to methods for performing a medical procedure, especially a procedure during which it is necessary to adjust the beating of the heart. More particularly, this invention relates to methods and systems of stimulating a nerve in order to modify the beating of a heart to allow a medical procedure to be performed or for blood flow to be controlled.

BACKGROUND OF THE INVENTION

The current leading cause of death in the United States is coronary artery disease in which the coronary arteries are blocked by atherosclerotic plaques or deposits of fat. The typical treatment to relieve a partially or fully blocked coronary artery is coronary artery bypass graph (CABG) surgery.

CABG surgery, also known as "heart bypass" surgery, generally entails using a graph to bypass the coronary obstruction. The procedure is generally lengthy, traumatic and subject to patient risks. Among the risk factors involved is the use of a cardiopulmonary bypass (CPB) circuit, also known as a "heart-lung machine," to pump blood and oxygenate the blood so that the patient's heart may be stopped during the surgery.

Conventional CABG procedures are typically conducted on a stopped heart while the patient is on a (CPB) circuit. A stopped heart and a CPB circuit enables a surgeon to work in a bloodless, still operative field. However, there are a number of problems associated with CABG procedures performed while on CPB including the initiation of a systemic inflammatory response due to interactions of blood elements with the artificial material surfaces of the CPB circuit and global myocardial ischemia due to cardioplegic cardiac arrest. For these reasons, avoiding the use of CPB or cardioplegic cardiac arrest may help minimize post-operative complications.

Additionally, it would be desirable to provide a method for controllably stopping or slowing the heart intermittently in order to perform a medical procedure on the heart or another organ.

Additionally, it would be desirable to provide a means for coordinating stimulation of the heart and other body components.

Additionally, it would be desirable to provide a means for evaluating the stimulation output from a variety of electrodes to determine the best stimulation configuration.

SUMMARY OF THE INVENTION

One aspect of the present invention provides a method for evaluating stimulation during a medical procedure. A site is stimulated with a first electrode arrangement. The stimulation at the site is then evaluated to provide a first stimulation value. The first electrode arrangement may comprise one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes, probe electrodes, cardiac stimulation electrodes, pacing electrodes and epicardial electrodes.

The method may also involve stimulating the site with a subsequent electrode arrangement and evaluating stimulation to provide a subsequent stimulation value. The first stimulation and subsequent stimulation values may be continued with the electrode arrangement associated with the best stimulation value. The subsequent electrode arrangement may comprise one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle

electrode arrangement may then be selected based on the first cardiac stimulation value and the subsequent cardiac stimulation value and the heart may be stimulated with the desired cardiac electrode arrangement. The first and subsequent cardiac electrode arrangements may be one or more electrodes such as nerve stimulation electrodes, cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes, patch electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, electrodes, epicardial electrodes, endotracheal electrodes and endoesophageal electrodes.

The method may also include delivering a drug such as a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotoninergic agonist, an antiarrythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin, methylxanthine, a P_2-purinoceptor agent, an ischemia agent, and a delta opioid agonist may be delivered during the procedure. The drug may be naturally occurring or chemically synthesized.

The nerve may be a nerve such as a vagal nerve, a carotid sinus nerve, a fat pad.

The medical procedure may be surgical procedures, non-surgical procedures, endoscopic procedures, fluoroscopic procedures, stent delivery procedures, aortic aneurysm repairs, cranial aneurysm repairs, delivery of drugs, delivery of biological agents, cardiac surgery with cardiopulmonary bypass circuits, cardiac surgery without cardiopulmonary bypass circuits, brain surgery, cardiograms, heart valve repair, heart valve replacement, MAZE procedures, revascularization procedures, transmyocardial revascularization, percutaneous myocardial revascularization, CABG procedures, anastomosis procedures, beating heart surgery, vascular surgery, neurosurgery, brain surgery, electrophysiology procedures, diagnostic procedures, therapeutic procedures,

electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes, probe electrodes, cardiac stimulation electrodes, pacing electrodes and epicardial electrodes.

The system may also include drug delivery means such as a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device for delivering drugs during the medical procedure.

Another aspect of the present invention provides a method of performing heart surgery. A nerve is stimulated with a first electrode arrangement to reduce the beating of a heart. Stimulation from the first electrode arrangement is evaluated to provide a first stimulation value. The nerve is then stimulated with a subsequent electrode arrangement and the stimulation is evaluated to provide a subsequent stimulation value. A desired electrode arrangement is selected based on the first stimulation value and the subsequent stimulation value and the nerve is stimulated with the desired electrode arrangement. The heart is then operated upon. Stimulation of the nerve is then stopped and the heart is stimulated to cause beating of the heart. The nerve is then re-stimulated to re-inhibit beating of the heart and the surgery is continued. The heart may also be stimulated with a first cardiac electrode arrangement to adjust the beating of the heart to the second condition. Stimulation from the first cardiac electrode arrangement may be evaluated to provide a first cardiac stimulation value. The heart may then be stimulated with a subsequent cardiac electrode arrangement and stimulation from this arrangement may be evaluated to provide a subsequent cardiac stimulation value. A desired cardiac electrode arrangement may then be selected based on the first cardiac stimulation value and the subsequent cardiac stimulation value and the heart may be stimulated with the desired cardiac electrode arrangement.

The foregoing, and other, features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims in equivalence thereof.

asystole (slowing or stopping of the heart's beating.) Once this induced asystole is stopped, i.e. once the vagal stimulation is stopped, the heart may be allowed to return to its usual cardiac rhythm. Alternatively, the heart may be paced with an electrical pacing system, thereby maintaining a normal cardiac output. Vagal stimulation, alone or in combination with electrical pacing, may be used selectively and intermittently to allow a surgeon to perform a medical procedure during intermittent periods of asystole.

It is known that stimulation of the vagus nerve can reduce the sinus rate, as well as prolong AV conduction time or, if stimulation energies are high enough, induce AV node block. Use of vagal nerve stimulation to treat supraventricular arrhythmias and angina pectoris is disclosed in the article "Vagal Tuning" by Bilgutay et al., Journal of Thoracic and Cardiovascular Surgery, Vol. 56, No. 1, July, 1968, pp. 71-82. It is also known that stimulation of the carotid sinus nerve produces a similar result, as disclosed in the article "Carotid Sinus Nerve Stimulation in the Treatment of Angina Pectoris and Supraventricular Tachycardia" by Braunwald et al., published in California Medicine, Vol. 112, pp. 41-50, March, 1970.

As set forth in "Functional Anatomy of the Cardiac Efferent Innervation" by Randall et al., in Neurocardiology, edited by Kulbertus et al, Futura Publishing Co., 1988, direct surgical excision of the fat pad associated with the SA node affects the functioning of the SA node without significantly affecting the AV node. Similarly, excision of the fat pad associated with the AV node affects functioning of the AV node without significantly affecting the SA node.

As set forth in the article "Parasympathetic Postganglionic Pathways to the Sinoatrial Node", Bluemel et al., Am. J. Physiol. 259, (Heart Circ. Physiol. 28) H1504-H1510, 1990, stimulation of the fat pad associated with the SA node results in slowing of the sinus rate without the accompanying prolongation of AV conduction time which normally results from vagal nerve stimulation. The article also indicates that stimulation of the fat pad associated with the AV node is believed to produce corresponding effects limited to the AV node, i.e., extension of the AV conduction time without concurrent slowing of the sinus rate.

As set forth in the article "Neural Effects on Sinus Rate and Atrial Ventricular Conduction Produced by Electrical Stimulation From a Transvenous Electrode Catheter in

may be configured to synchronize activation and deactivation of breathing regulator **240** with vagal stimulation, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Nerve stimulator **210** may be connected to a surgeon controlled switch box. A switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the nerve stimulator **210** by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to alert a surgeon to the completion or resumption of stimulation may be incorporated into nerve stimulator **210**. For example, a beeping tone or flashing light that increases in frequency as the stimulation period should end or begin may be used.

Nerve stimulator **210** may be slaved to cardiac stimulator **220** or cardiac stimulator **220** may be slaved to nerve stimulator **210**. For example, the output of cardiac stimulator **220** may be off whenever the output of nerve stimulator **210** is on. Software controlling cardiac stimulator **220** may be designed to automatically commence cardiac pacing if the heart does not resume beating within a pre-determined interval after cessation of vagal nerve stimulation. In addition, the software controlling nerve stimulator **210** may be designed to automatically stop vagal nerve stimulation if the heart has been stopped for too long.

The application of an electrical stimulus to the right or left vagal nerve may include, but is not limited to bipolar and/or monopolar techniques. Nerve stimulation electrodes may be positioned within the body of a patient, positioned on the skin of a patient and/or in combinations thereof. Electrical stimulation may be carried out on the right vagal nerve, the left vagal nerve or to both nerves simultaneously or sequentially. The present invention may include various electrodes, suitable for vagal nerve stimulation to temporarily stop or slow the beating heart alone or in combination with other heart rate inhibiting agents.

Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of electrodes. In one embodiment of the present invention, the location of the vagal nerve stimulation electrodes is chosen to elicit maximum

metal foil, metal wire and/or conductive plastic. The electrodes may be used in a monopolar and/or bipolar arrangement. For example, two electrodes on the cannula may be used in a bipolar fashion or one electrode on the cannula may be used in a monopolar fashion in combination with an external skin electrode.

FIG. 2 shows one embodiment of an electrode device comprising endotracheal electrodes in accordance with the present invention at **10A**. Electrode device **10A** may comprise a tube **100** suitable for insertion through a patient's nose or mouth and into the patient's trachea.

Electrode device **10A** may include a first electrode arrangement attached to tube **100**. This electrode arrangement may be used to accomplish stimulation on such body components as nerves, muscles, the heart, and the lungs. This stimulation may be used to controllably stop or start an organ such as the heart or lungs or to ease pain. The electrode arrangement may also be used to sense or monitor physiological functions.

Tube **100** may comprise a flexible, non-electrically conducting tube having a proximal end **11** and a distal end **12**. Tube **100** may be made of a material selected for its stiffness and flexibility to allow tube **100** to conform readily to the shape of the patient's trachea with minimal trauma to tissue. For example, silicone rubber, polyurethane or other polymers or materials may be used. The outer diameter and length of tube **100** may vary depending upon size of the patient for whom it is intended. Lubricating gels or creams may be used during placement of the device. These lubricating gels or creams may or may not be conductive. Tube **100** may include a biocompatible coating, for example, a slip coating for easier insertion.

Tube **100** may also include main lumen **20** for transporting gases to and from the lungs. Main lumen **20** runs from the proximal end of tube **100** to the distal end of tube **100**. Tube **100** may be connected at proximal end **11** to a breathing regulator, which injects and withdraws air from the lungs. Proximal end **11** may include a standard tracheal tube adapter for anesthesia gas connection. Proximal end **11** may include a stop which engages the face of the patient so as to prevent further insertion when the distal end is in the proper location.

An inflatable cuff **13** may be located near distal end **12** of tube **100**. Inflatable cuffs are typically used on tracheal tubes to prevent air from escaping by passing between

100 and a second electrode arrangement attached to collar 101. These electrode arrangements may be used to accomplish stimulation on such body components as nerves, muscles, the heart, and the lungs. This stimulation may be used to controllably stop or start an organ such as the heart or lungs or to ease pain. The electrodes may also be used to sense or monitor physiological functions.

Collar 101 may comprise a flexible, non-electrically conducting material selected for its stiffness and flexibility to allow collar 101 to conform readily to the shape of the patient's neck. The collar may be adjustable to allow it to fit appropriately the neck size of the patient for whom it is intended. Associated with collar 101 is an arrangement of electrodes 116. These electrodes may comprise an electrically conducting material, for example, metal paint, metal tape, metal strips, metal buttons, metal foil, metal wire and/or conductive plastic. The electrodes may be wire electrodes, button electrodes and/or foil electrodes. The electrodes may be arranged circumferentially around the neck of a patient. Collar 101 may comprise one or more electrodes. Conductive gels or creams may be used in combination with the collar to help improve electrical contact of electrodes 116 with the body of the patient.

FIG. 4 shows one embodiment of an electrode device comprising endotracheal electrodes in accordance with the present invention at 10C. Electrode device 10C may comprise tube 100, for example, as described above, and one or more external electrodes 102. Electrodes 102 may be suitable for external placement on a portion of the body such as, for example, on the neck or chest. Electrode device 10C may include a first electrode arrangement attached to tube 100 and a second electrode arrangement external to the patient's body, for example external electrode 102. Electrode arrangement 102 may comprise one or more typical external electrodes, for example skin or patch electrodes. The first and second electrode arrangements may be used to accomplish stimulation on such body components as nerves, muscles, the heart, and the lungs. This stimulation may be used to controllably stop or start an organ such as the heart or lungs or to ease pain. The electrodes may also be used to sense or monitor physiological functions.

In Fig. 4, tube 100 is shown comprising an arrangement of metal wire electrodes 16 located on the outer surface of inflatable cuff 13. In this particular embodiment, electrodes 16 are shown as wires that run from a location between the two tube ends 11

other polymers or materials may be used. The outer diameter and length of tube **103** may vary depending upon size of the patient for whom it is intended. Lubricating gels or creams may be used during placement of the device. These lubricating gels or creams may or may not be conductive. Tube **103** may include a biocompatible coating, for example, a slip coating for easier insertion. Tube **103** may include positioning marks or other positioning technologies.

Associated with tube **103** is an arrangement of electrodes **16**. These electrodes may comprise an electrically conducting material, for example, metal paint, metal tape, metal strips, metal buttons, metal foil, metal wire and/or conductive plastic. The electrodes may be ring electrodes, wire electrodes, button electrodes and/or foil electrodes. The electrodes may be used in a monopolar and/or bipolar arrangement. For example, two electrodes on tube **103** may be used in a bipolar fashion or one electrode on tube **103** may be used in a monopolar fashion in combination with an external skin electrode **102**. The electrodes may be arranged parallel to the axis of tube **103** and/or the electrodes may be arranged circumferentially to the axis of tube **103**. Tube **103** may comprise one or more electrodes. The electrodes may be located proximal to an inflatable cuff or hole, distal to an inflatable cuff or hole, on one or more inflatable cuffs and/or combinations thereof. For example, in **FIG. 5**, electrode arrangement **16** comprises an array of wire electrodes wrapped around the outer surface of tube **103** and arranged around multiple holes **14**.

One or more holes **14** in tube **103** in the area of the electrodes **16** provides a means of ensuring better electrical contact with the esophageal wall and electrodes **16** when suction is introduced through suction conduit **18**. Suction conduit **18** may be attached to a vacuum source. Suction conduit **18** may be a lumen which communicates with one or more holes **14** through a port in tube **103**. A variety of securing means besides holes **14** may be used for improving electrical contact between electrodes and esophageal wall, for example suction pods or a sticky biocompatible substance may be used.

FIG. 6 shows one embodiment of an electrode device comprising esophageal electrodes in accordance with the present invention at **10E**. Electrode device **10E** may comprise a tube **103** suitable for insertion through a patient's nose or mouth and into the patient's esophagus. Electrode device **10D** may comprise one or more external electrodes **102** as described above.

Cardiac stimulator **220** may also comprise any conventional pacing device suitable for ventricular demand pacing.

Cardiac stimulator **220** may be combined in a single unit with a switch box. Cardiac stimulator **220** may comprise a surgeon controlled switch box. A switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the cardiac stimulator by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies. A single switch may be used to regulate both cardiac stimulator **220** and nerve stimulator **210**.

A visual and/or audible signal used to prepare a surgeon for the resumption of pacing may be incorporated into cardiac stimulator **220**. For example, a beeping tone or flashing light that increases in frequency as the pacing period ends may be used. A single signaling method or device may be used for both cardiac stimulator **220** and nerve stimulator **210**.

Cardiac stimulator **220** may comprise any type of electrodes suitable for stimulating the heart, for example, non-invasive electrodes, e.g., clips, or invasive electrodes, e.g., needles or probes may be used. Cardiac stimulation electrodes may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the chest, placed on the chest or in combinations thereof. The present invention may also use various electrodes, catheters and electrode catheters suitable for pacing the heart, e.g., epicardial, endocardial, patch-type, intravascular, balloon-type, basket-type, umbrella-type, tape-type electrodes, suction-type, pacing electrodes, endotracheal electrodes, esophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, catheter sheath electrodes, introducer electrodes, cannula electrodes and cuff electrodes. The electrodes may comprise an electrically conducting material, for example, metal paint, metal tape, metal strips, metal buttons, metal foil, metal wire and/or conductive plastic. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the electrodes.

limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision, placed on the skin or in combinations thereof. The present invention may include various electrodes, catheters and electrode catheters suitable for phrenic nerve stimulation to control breathing.

Phrenic nerve stimulation electrodes may be intravascular, patch-type, balloon-type, basket-type, umbrella-type, tape-type, cuff-type, suction-type, screw-type, barb-type, bipolar, monopolar, metal, wire, endotracheal electrodes, esophageal electrodes, intravascular electrodes, transcutaneous electrodes, catheter sheath electrodes, introducer electrodes, cannula electrodes or intracutaneous electrodes. The electrodes may comprise an electrically conducting material, for example, metal paint, metal tape, metal strips, metal buttons, metal foil, metal wire and/or conductive plastic. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be used. The catheter may comprise, for example, a balloon that may be inflated with air or liquid to press the electrodes firmly against a vessel wall that lays adjacent the phrenic nerve.

Phrenic nerve stimulation electrodes may be oriented in any fashion along a device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters that incorporate one or more tunnels or passageways.

In another embodiment, the breathing regulator may comprise a connector that interfaces with a patient's respirator, and sends a logic signal to activate or deactivate the respirator to control breathing during vagal and/or cardiac stimulation and/or destimulation.

System **200** may also include electrodes for relieving pain such as indicated at 260. In one embodiment, pain-relieving electrodes may be used to stimulate the spinal cord.

cardiac stimulation or pain relieving and/or they may be positioned adjacent one or more of the sites of stimulation described above.

System **200** may also include controller **230**. Controller **230** may be used to gather information from nerve stimulator **210** and cardiac stimulator **220**. Controller **230** may also be used to control the stimulation levels and stimulation duration of nerve stimulator **210** and cardiac stimulator **220**. Controller **230** may also gather and process information from the various components of system **200**, in particular sensing electrodes **270**. This information may be used to adjust stimulation levels and stimulation times of nerve stimulator **210**, cardiac stimulator **220**, breathing regulator **240** and/or pain relieving electrodes **260**. This adjustment may be based, for example, on data received from monitoring electrodes **270**.

System **200** may incorporate one or more switches to facilitate regulation of the various components by the surgeon. One such switch is indicated schematically at **250**. The switch may be, for example, a hand switch, a foot switch or a voice-activated switch comprising voice-recognition technologies. The switch may be incorporated on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon.

System **200** may also incorporate means for indicating the status of various components to the surgeon such as feedback means **280**. These feedback means may comprise a display, a numerical display, gauges, a monitor display or audio feedback. Feedback means **280** may also comprise one or more visual and/or audible signals used to prepare a surgeon for the start or stop of nerve stimulation and/or cardiac stimulation. Alternatively, the feedback means may be incorporated on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon.

FIG. 7 shows a flow diagram of one embodiment of the present invention at **300**. Stimulation from at least one electrode of a first electrode arrangement may begin at block **310**. In one embodiment of the invention, the first electrode arrangement may be located on tube **100** of device **10**. At block **320**, stimulation from at least one electrode of a second electrode arrangement is begun. In one embodiment of the invention, the second electrode arrangement may be located on collar **101** of device **10**. At block **330**, data is

and/or inhalation delivery. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include a oil, sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered.

Drug formulations or compositions may include antioxidants or preservatives such as ascorbic acid. Other preservatives include benzalkonium chloride, methyl-paraben, propyl-paraben, and chlorbutanol. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent. Drugs may be administered, for example, systemically or locally, for example, to the heart, to a coronary artery and/or vein, to a pulmonary artery and/or vein, to the right atrium and/or ventricle, to the left atrium and/or ventricle, to the aorta, to the AV node, to the SA node, to a nerve and/or to the coronary sinus. Drugs may be administered or delivered via intravenous, intracoronary and/or intraventricular administration in a suitable carrier. Examples of arteries that may be used to deliver drugs to the AV node include the AV node artery, the right coronary artery, the right descending coronary artery, the left coronary artery, the left anterior descending coronary artery and Kugel's artery. Drugs may be delivered systemically, for example, via oral, transdermal, intranasal, suppository or inhalation methods. Drugs also may be delivered via a pill, a spray, a cream, an ointment or a medicament formulation.

Drugs may be delivered via a drug delivery device that may comprise a catheter, such as a drug delivery catheter or a guide catheter, a patch, such as a transepicardial patch that slowly releases drugs directly into the myocardium, a cannula, a pump and/or a

Since beta-adrenergic receptors are concerned with contractility and heart rate, stimulation of beta-adrenergic receptors, in general, increases heart rate, the contractility of the heart and the rate of conduction of electrical impulses through the AV node and the conduction system.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) beta-adrenergic receptor blocking agents. Beta-adrenergic receptor blocking agents or □-adrenergic blocking agents are also known as beta-blockers or □-blockers and as class II antiarrhythmics.

The term "beta-blocker" appearing herein may refer to one or more agents that antagonize the effects of beta-stimulating catecholamines by blocking the catecholamines from binding to the beta-receptors. Examples of beta-blockers include, but are not limited to, acebutolol, alprenolol, atenolol, betantolol, betaxolol, bevantolol, bisoprolol, carterolol, celiprolol, chlorthalidone, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, oxprenolol, sotalol, teratolol, timolol and combinations, mixtures and/or salts thereof.

The effects of administered beta-blockers may be reversed by administration of beta-receptor agonists, e.g., dobutamine or isoproterenol.

The parasympathetic or cholinergic system participates in control of heart rate via the sinoatrial (SA) node, where it reduces heart rate. Other cholinergic effects include inhibition of the AV node and an inhibitory effect on contractile force. The cholinergic system acts through the vagal nerve to release acetylcholine, which, in turn, stimulates cholinergic receptors. Cholinergic receptors are also known as muscarinic receptors. Stimulation of the cholinergic receptors decreases the formation of cAMP. Stimulation of cholinergic receptors generally has an opposite effect on heart rate compared to stimulation of beta-adrenergic receptors. For example, beta-adrenergic stimulation increases heart rate, whereas cholinergic stimulation decreases it. When vagal tone is high and adrenergic tone is low, there is a marked slowing of the heart (sinus bradycardia). Acetylcholine effectively reduces the amplitude, rate of increase and duration of the SA node action potential. During vagal nerve stimulation, the SA node does not arrest. Rather, pacemaker function may shift to cells that fire at a slower rate. In addition,

There are ion-selective channels within certain cell membranes. These ion selective channels include calcium channels, sodium channels and/or potassium channels. Therefore, other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized calcium channel blocker. Calcium channel blockers inhibit the inward flux of calcium ions across cell membranes of arterial smooth muscle cells and myocardial cells. Therefore, the term "calcium channel blocker" appearing herein may refer to one or more agents that inhibit or block the flow of calcium ions across a cell membrane. The calcium channel is generally concerned with the triggering of the contractile cycle. Calcium channel blockers are also known as calcium ion influx inhibitors, slow channel blockers, calcium ion antagonists, calcium channel antagonist drugs and as class IV antiarrhythmics. A commonly used calcium channel blocker is verapamil.

Administration of a calcium channel blocker, e.g., verapamil, generally prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner, since the electrical activity through the AV node depends significantly upon the influx of calcium ions through the slow channel. A calcium channel blocker has the ability to slow a patient's heart rate, as well as produce AV block. Examples of calcium channel blockers include, but are not limited to, amiloride, amlodipine, bepridil, diltiazem, felodipine, isradipine, mibefradil, nicardipine, nifedipine (dihydropyridines), nickel, nimodinpine, nisoldipine, nitric oxide (NO), norverapamil and verapamil and combinations, mixtures and/or salts thereof. Verapamil and diltiazem are very effective at inhibiting the AV node, whereas drugs of the nifedipine family have a lesser inhibitory effect on the AV node. Nitric oxide (NO) indirectly promotes calcium channel closure. NO may be used to inhibit contraction. NO may also be used to inhibit sympathetic outflow, lessen the release of norepinephrine, cause vasodilation, decrease heart rate and decrease contractility. In the SA node, cholinergic stimulation leads to formation of NO.

Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized sodium channel blocker. Sodium channel blockers are also known as sodium channel inhibitors, sodium channel blocking agents, rapid channel blockers or rapid channel inhibitors. Antiarrhythmic agents that inhibit or block the sodium channel are known as

Potassium is the most common component in cardioplegic solutions. High extracellular potassium levels reduce the membrane resting potential. Opening of the sodium channel, which normally allows rapid sodium influx during the upstroke of the action potential, is therefore inactivated because of a reduction in the membrane resting potential. The present invention may be combined with conventional CPB, the induced asystole as described by this invention may serve as a substitute for conventional cardioplegic arrest. For example, the combination of drugs and vagal stimulation may be used as a cardioplegic agent in a variety of medical procedures.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) ischemia agents. The term "ischemia agent" appearing herein may refer to one or more agents that protect one or more organs and/or tissues from ischemic damage. For example, delta opioid receptor modulators, mediators, agonists and/or antagonists as disclosed in U.S. Patent No. 6,103,722 to inventors Schultz and Gross and in U.S. Patent No. 5,656,420 to inventor Chien have been used in ischemia protection.

Although it is desirable to stop the heart for a period of time in order to allow the surgeon to accomplish a required task without interference from heart movement, stopping the heart for prolonged periods of time may cause damage to various organs and tissues from ischemia or lack of oxygen. Opioid receptor activation on organs and tissues which possess delta opioid receptors has been shown to elicit a protective effect during periods of ischemia. Delivering an ischemia agent such as a delta opioid agonist to the patient may protect certain organs and tissues such as cardiac and/or brain tissue of the patient from ischemic damage caused by intermittent periods of cardiac asystole. Examples of delta opioid agonists include, but are not limited to, TAN67(-), DPDPE, BW373U86, DADLE, SB219825, SNC80 and SIOM and combinations, mixtures and/or salts thereof.

Drugs, drug formulations and/or drug compositions that may be used during according to this invention may comprise one or more of any naturally occurring or chemically synthesized beta-blocker, cholinergic agent, cholinesterase inhibitor, calcium channel blocker, sodium channel blocker, potassium channel agent, adenosine, adenosine receptor agonist, adenosine deaminase inhibitor, dipyridamole, monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, bradykinin agents, serotoninergic agonist,

cardiopulmonary bypass (CPB) circuits, heart valve repair, heart valve replacement, MAZE procedures,revascularization procedures, transmyocardial revascularization (TMR) procedures, percutaneous myocardial revascularization (PMR) procedures, CABG procedures, anastomosis procedures, non-surgical procedures, fluoroscopic procedures, beating heart surgery, vascular surgery, neurosurgery, brain surgery, electrophysiology procedures, diagnostic and therapeutic procedures, ablation procedures, ablation of arrhythmias, endovascular procedures, treatment of the liver, spleen, heart, lungs, and major blood vessels, aneurysm repair, imaging procedures of the heart and great vessels, CAT scans or MRI procedures, pharmacological therapies, drug delivery procedures, gene therapies, cellular therapies, cancer therapies, radiation therapies, genetic, cellular, tissue and/or organ manipulation or transplantation procedures, coronary angioplasty procedures, placement or delivery of coated or noncoated stents, atherectomy procedures, atherosclerotic plaque manipulation and/or removal procedures, procedures where bleeding needs to be precisely controlled, procedures that require precise control of cardiac motion and/or bleeding.

When the medical procedure comprises one or more medical devices, e.g., coated stents, these devices may be coated with one or more radioactive materials and/or biological agents such as, for example, an anticoagulant agent, an antithrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defense agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein, a peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent, a bacterial agent or component, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a lectin, an antiviral agent, a viral agent or component, a genetic agent, a ligand and a dye (which acts as a biological ligand). Biological agents may be found in nature (naturally occurring) or may be chemically synthesized.

The medical procedure may be non-invasive, minimally invasive and/or invasive. The medical procedure may entail a port-access approach, a partially or totally endoscopic approach, a sternotomy approach or a thoracotomy approach. The medical procedure may

described above. Therefore from Block **530** or Block **535**, the method may be repeated (Block **540**). For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (Block **510**). Again, the stimulation electrodes may be evaluated using the routine of the present invention to find the optimal stimulation arrangement. Additional drugs may be delivered or the drugs previously administered may continue to be administered.

Additional surgery, additional steps in the medical procedure or additional medical procedures may again be performed (Block **520**) while the heart is still. Then, this stage of stillness may be followed by another stage when the stimulation is removed (Block **530**) and the heart is allowed to contract. Again, the heart may be stimulated to encourage contractions (Block **535**). Again, the stimulation electrodes may be evaluated using the routine of the present invention to find the optimal stimulation arrangement.

This cycle may be repeated until the procedure, such as the surgery, is completed. After the procedure is completed, step **535** may be performed until the heart is beating normally. At the procedure's end, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered for example to alleviate pain or aid in recuperation. Other drugs may be administered for a variety of functions and purposes as described above.

For example, a surgical procedure at **520** may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at **510** to stop the heart. Then the surgeon may make the first stitch at **520**. The surgeon may then reduce or halt stimulation at **530** and allow the heart to contract. The surgeon may also pace the heart at **535**. Then at **540**, the surgeon may return to **510** to inhibit contractions of the heart. At **520**, the surgeon will then make the second stitch. This process may be repeated (the loop designated by **540** may be repeated) until all the required stitches have been made.

FIG. 9 is a timeline showing the relation of the vagal nerve stimulation to the cardiac stimulation in one embodiment of the present invention.

Point **610** indicates a point before the medical procedure has begun. At this point **610**, both nerve stimulation and cardiac stimulation are off. At point **610**, the heart is beating regularly. Then nerve stimulation is turned on to inhibit beating of the heart. At point **610**, the stimulation electrodes used to stimulate the nerve may be evaluated

WE CLAIM:

1. A method of evaluating stimulation during a medical procedure, comprising:

stimulating a site with a first electrode arrangement; and

evaluating stimulation at the site to provide a first stimulation value.

2. A method of claim 1 wherein the first electrode arrangement comprises at least one electrode selected from the group consisting of:

nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes, and probe electrodes.

3. A method of claim 1 wherein the first electrode arrangement comprises at least one electrode selected from the group consisting of:

cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes and epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, and cuff electrodes.

4. The method of claim 1 further comprising:

stimulating the site with a subsequent electrode arrangement;

evaluating stimulation at the site to provide a subsequent stimulation value;

evaluating stimulation from the subsequent electrode arrangement to provide a subsequent stimulation value;

selecting a desired electrode arrangement based on the first stimulation value and the subsequent stimulation value; and

stimulating the nerve with the desired electrode arrangement.

8. A method of claim 7 wherein the first electrode arrangement comprises at least one electrode selected from the group consisting of:

nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes, and probe electrodes.

9. A method of claim 7 wherein the first electrode arrangement comprises at least one electrode selected from the group consisting of:

cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes and epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, and cuff electrodes.

10. A method of claim 7 wherein the subsequent electrode arrangement comprises at least one electrode selected from the group consisting of:

nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar

17. The method of claim 7 wherein the stimulation is stopped to achieve the second condition.

18. The method of claim 12 wherein the second condition is a beating condition.

19. The method of claim 12 further comprising:

stimulating the heart in order to adjust the beating of the heart to the second condition.

20. The method of claim 12 further comprising:

stimulating the heart with a first cardiac electrode arrangement to adjust the beating of the heart to the second condition;

evaluating stimulation from the first cardiac electrode arrangement to provide a first cardiac stimulation value;

stimulating the heart with a subsequent cardiac electrode arrangement;

evaluating stimulation from the subsequent cardiac electrode arrangement to provide a subsequent cardiac stimulation value;

selecting a desired cardiac electrode arrangement based on the first cardiac stimulation value and the subsequent cardiac stimulation value; and

stimulating the heart with the desired cardiac electrode arrangement.

21. A method of claim 12 wherein the first cardiac electrode arrangement comprises at least one electrode selected from the group consisting of:

cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes and epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes,

27. The method of claim 23 wherein the nerve is selected from the group consisting of:

a vagal nerve, a carotid sinus nerve, a fat pad.

28. The method of claim 7 wherein the medical procedure is selected from the group consisting of:

surgical procedures, non-surgical procedures, endoscopic procedures, fluoroscopic procedures, stent delivery procedures, aortic aneurysm repairs, cranial aneurysm repairs, delivery of drugs, delivery of biological agents, cardiac surgery with cardiopulmonary bypass circuits, cardiac surgery without cardiopulmonary bypass circuits, brain surgery, cardiograms, heart valve repair, heart valve replacement, MAZE procedures, transmyocardial revascularization, CABG procedures, beating heart surgery, vascular surgery, neurosurgery, electrophysiology procedures, diagnostic ablation of arrhythmias, therapeutic ablation of arrhythmias, endovascular procedures, treatment of injuries to the liver, treatment of the spleen, treatment of the heart, treatment of the lungs, treatment of major blood vessels, non-invasive procedures, invasive procedures, and port-access procedures.

29. A device for performing a medical procedure, comprising:

a first electrode arrangement operatively arranged on a stimulation tube; and

a second electrode arrangement operatively arranged on a stimulation collar.

30. A device of claim 29 wherein the first electrode arrangement comprises at least one electrode selected from the group consisting of:

nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes,

electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, and cuff electrodes.

34. The device of claim 29 further comprising:

a processor for evaluating stimulation from a set of electrodes, the pair of electrodes comprising at least one electrode from the stimulation tube and at least one electrode from the stimulation collar.

35. The device of claim 34 further comprising:

a drug pump for delivering at least one drug, the drug pump operatively connected to the processor wherein the processor adjusts the output of the drug.

36. A system for performing a medical procedure, comprising:

a first electrode arrangement operatively arranged on a stimulation tube;

a second electrode arrangement operatively arranged on a stimulation collar;

a processor for evaluating stimulation from a set of electrodes, the pair of electrodes comprising at least one electrode from the stimulation tube and at least one electrode from the stimulation collar;

a controller for controlling stimulation from the set of electrodes.

37. A system of claim 36 wherein the first electrode arrangement comprises at least one electrode selected from the group consisting of:

nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes, and probe electrodes.

drug delivery means for delivering drugs during the medical procedure.

42. The system of claim 41 wherein the drug delivery means is selected from the group consisting of:

a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device.

43. A method of performing heart surgery, comprising:

transvenously stimulating a nerve with a first electrode arrangement to reduce the beating of a heart;

evaluating stimulation from the first electrode arrangement to provide a first stimulation value;

stimulating the nerve with a subsequent electrode arrangement;

evaluating stimulation from the subsequent electrode arrangement to provide a subsequent stimulation value;

selecting a desired electrode arrangement based on the first stimulation value and the subsequent stimulation value; and

stimulating the nerve with the desired electrode arrangement;

performing surgery on the heart;

stopping stimulation of the nerve;

stimulating the heart to cause beating of the heart;

re-stimulating the nerve to re-inhibit beating of the heart; and

continuing the surgery.

44. The method of claim 43 further comprising:

stimulating the heart with a first cardiac electrode arrangement to adjust the beating of the heart to the second condition;

evaluating stimulation from the first cardiac electrode arrangement to provide a first cardiac stimulation value;

stimulating the heart with a subsequent cardiac electrode arrangement;

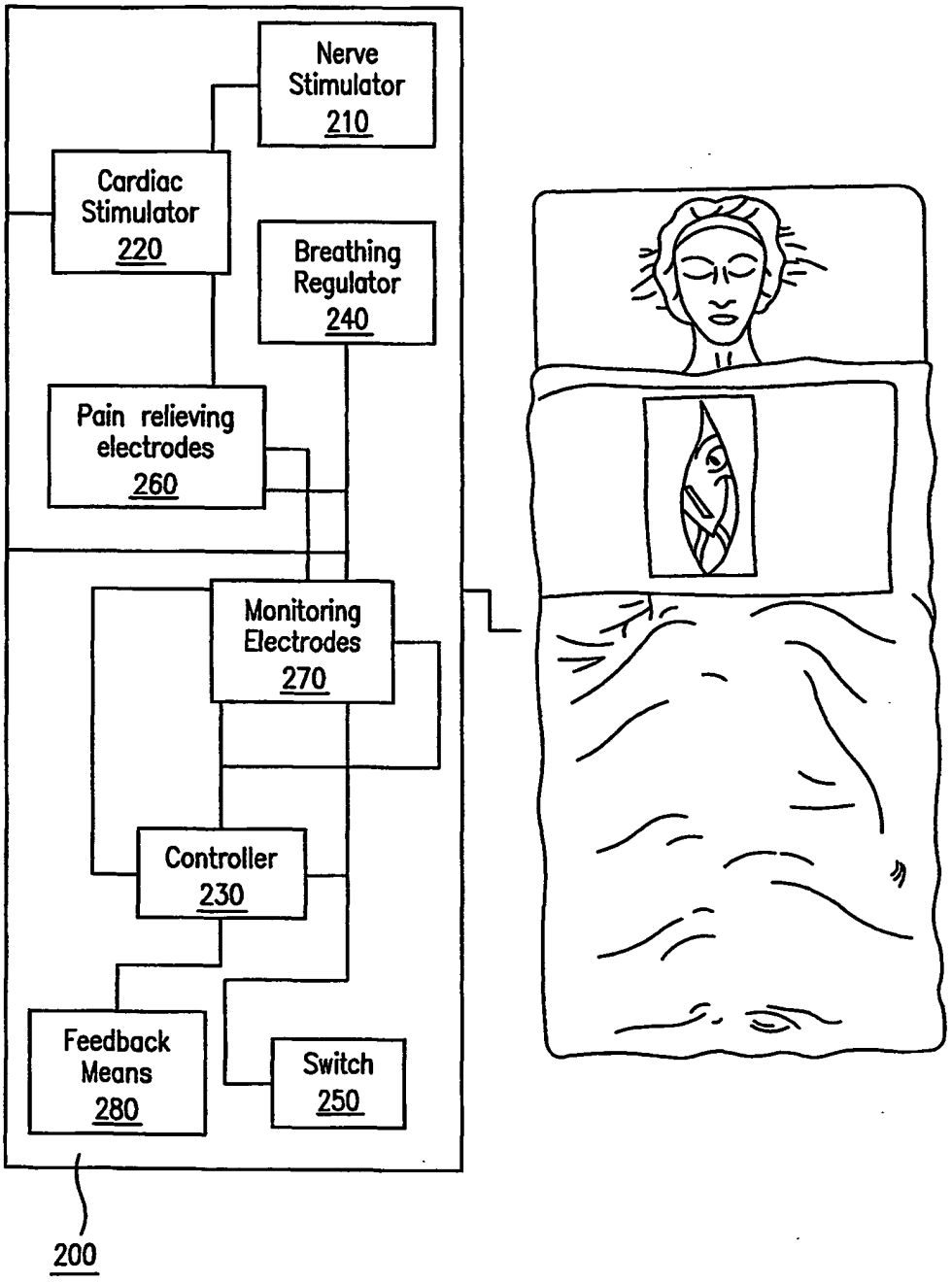
Nerve Stimulator 210
Cardiac Stimulator 220
Breathing Regulator 240
Pain relieving electrodes 260
Monitoring Electrodes 270
Controller 230
Feedback Means 280
Switch 250
200

FIG. 1

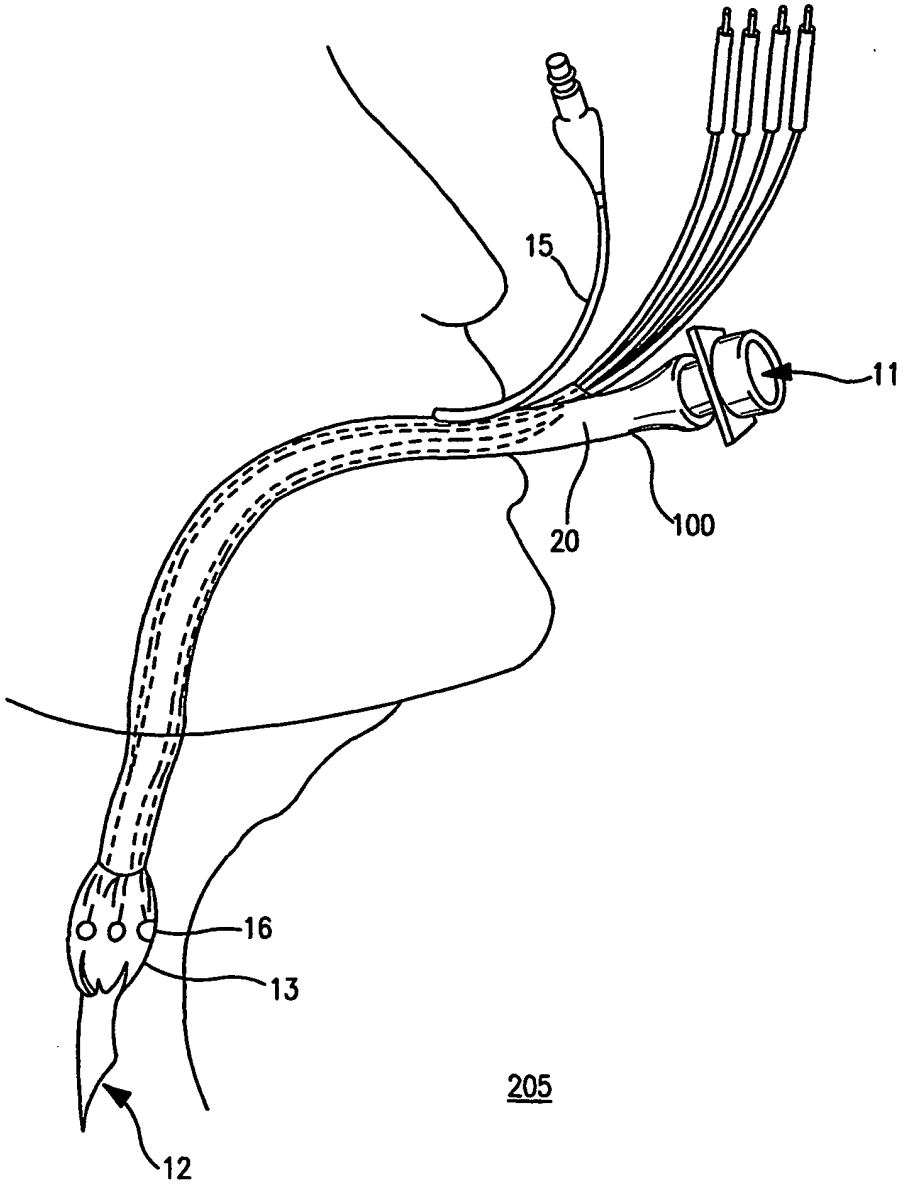

FIG. 2

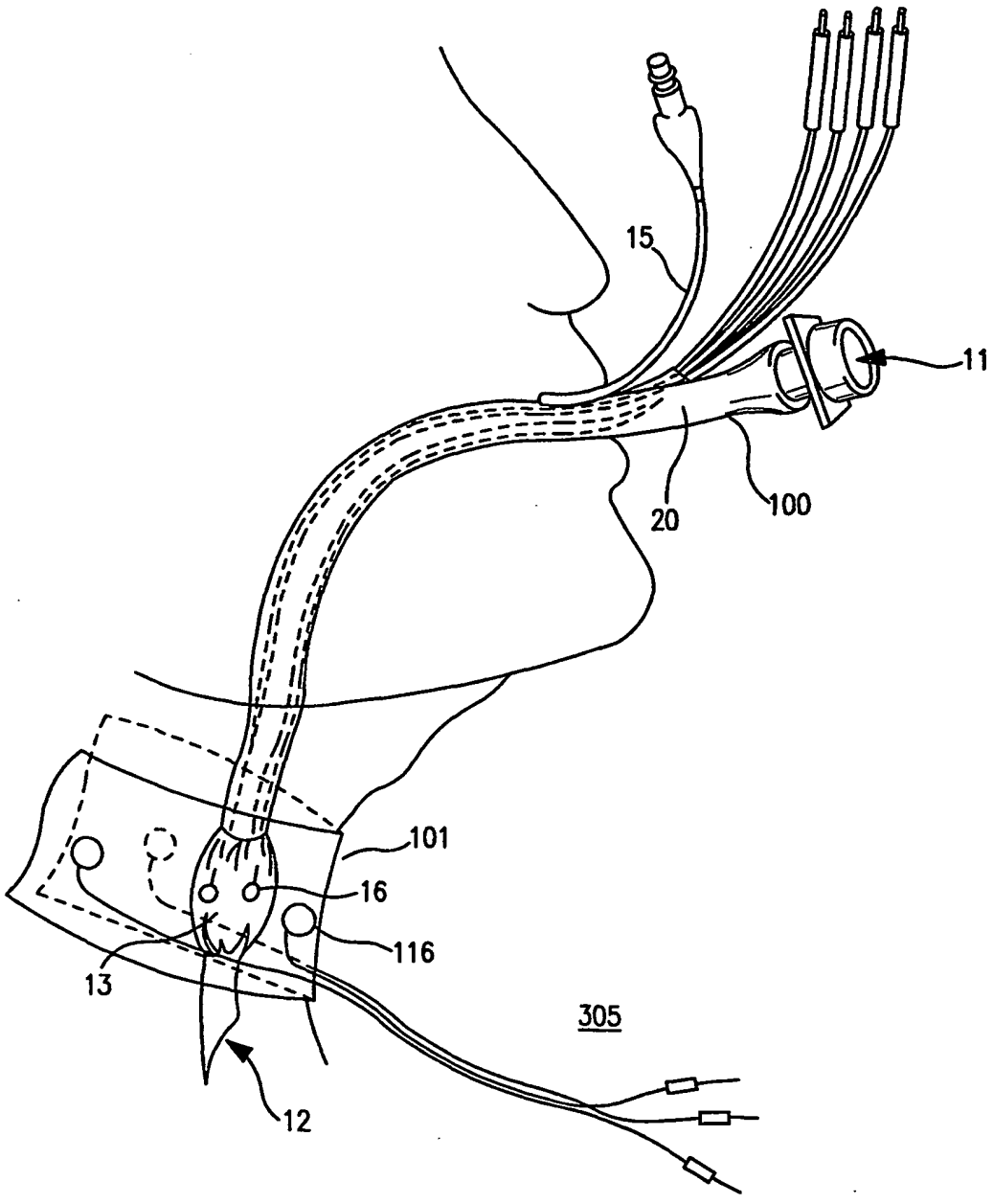

FIG. 3

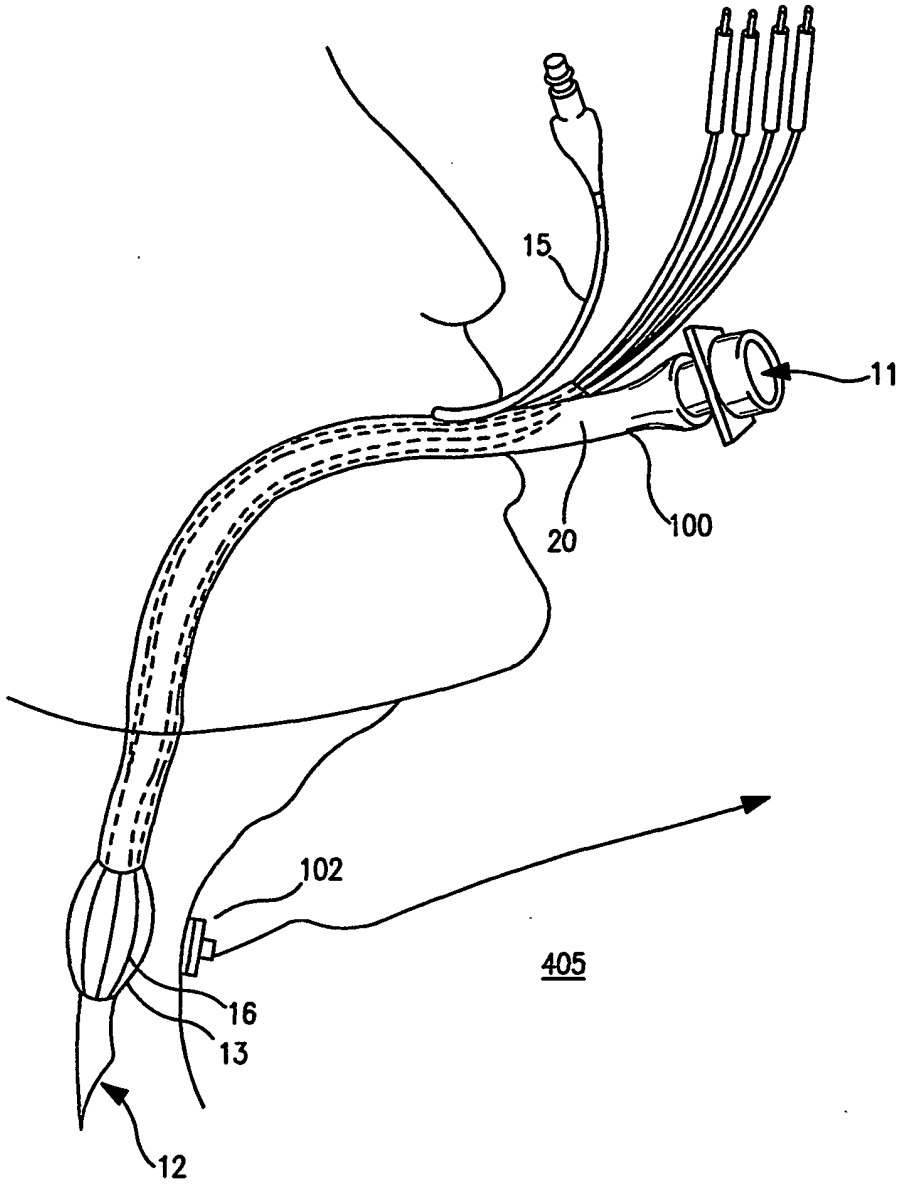

FIG. 4

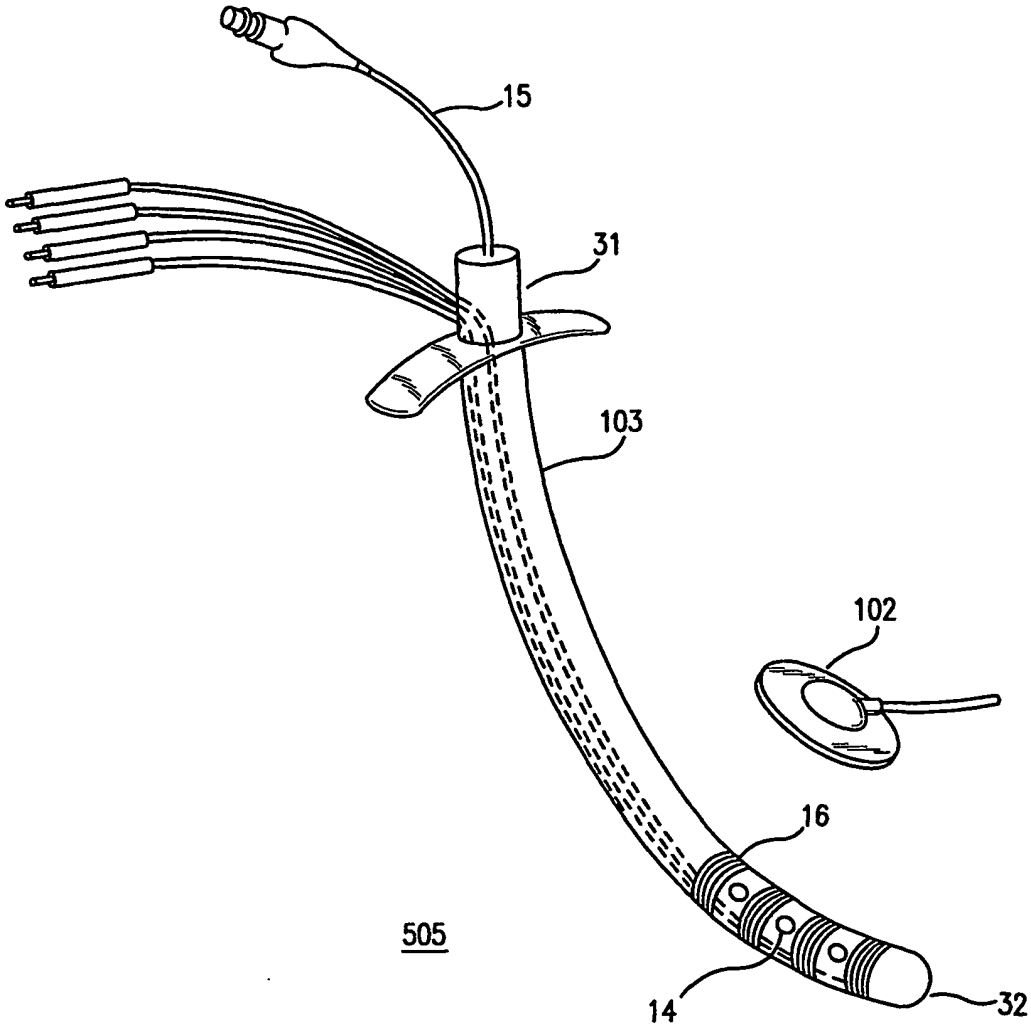

FIG. 5

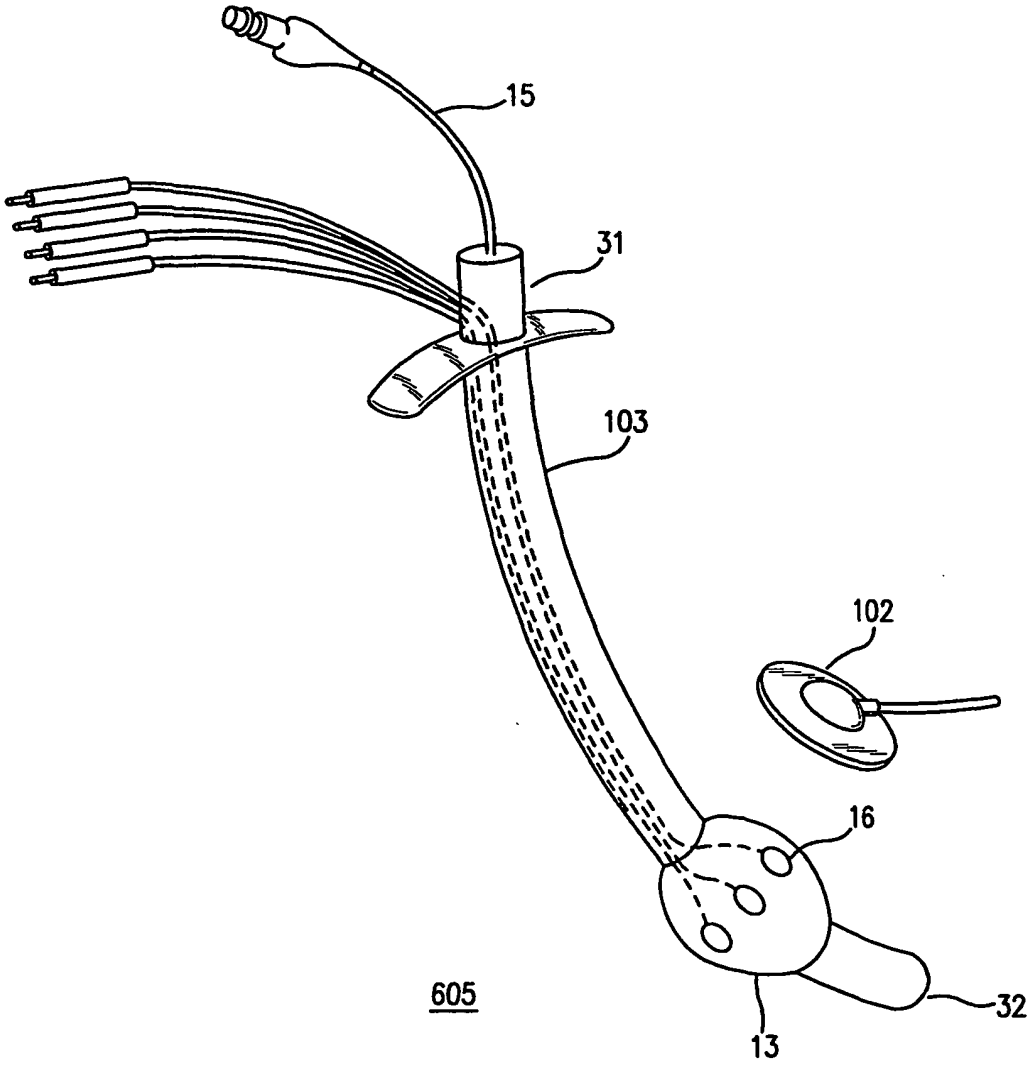

FIG. 6

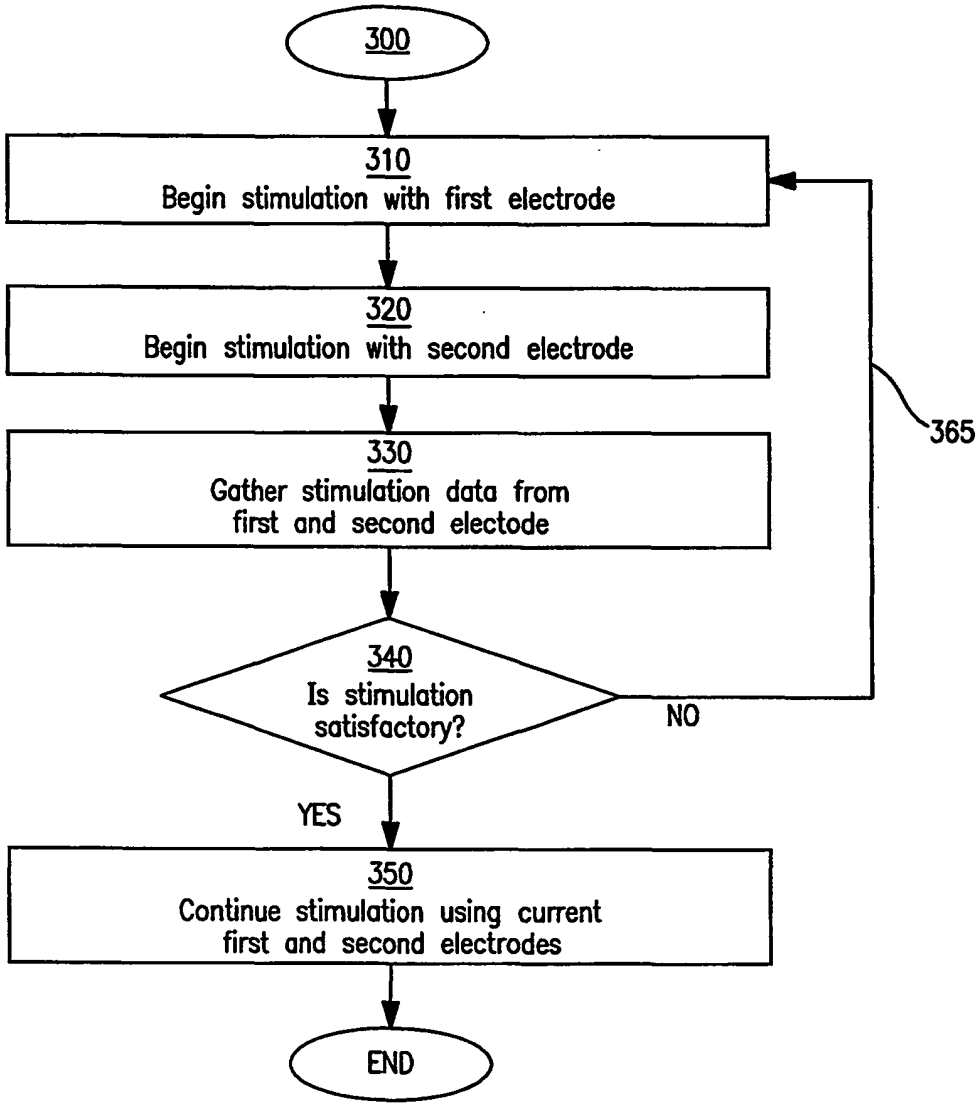
300
310
Begin stimulation with first electrode
320
Begin stimulation with second electrode
330
Gather stimulation data from first and second electode
340
Is stimulation satisfactory?
NO
365
YES
350
Continue stimulation using current first and second electrodes
END

FIG. 7

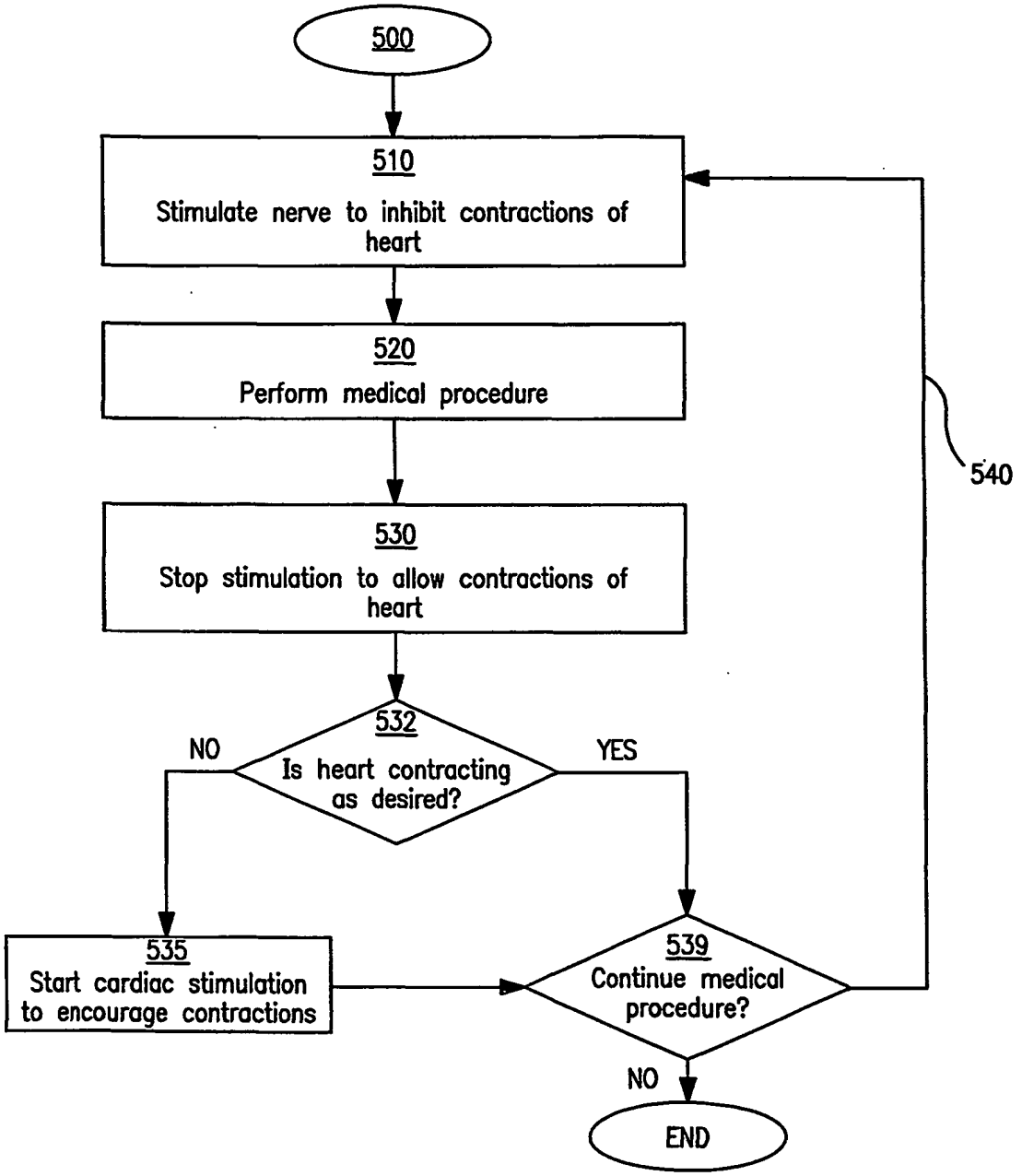
500
510
Stimulate nerve to inhibit contractions of heart
520
Perform medical procedure
530
Stop stimulation to allow contractions of heart
532
Is heart contracting as desired?
NO
YES
535
Start cardiac stimulation to encourage contractions
539
Continue medical procedure?
NO
END
540

FIG. 8

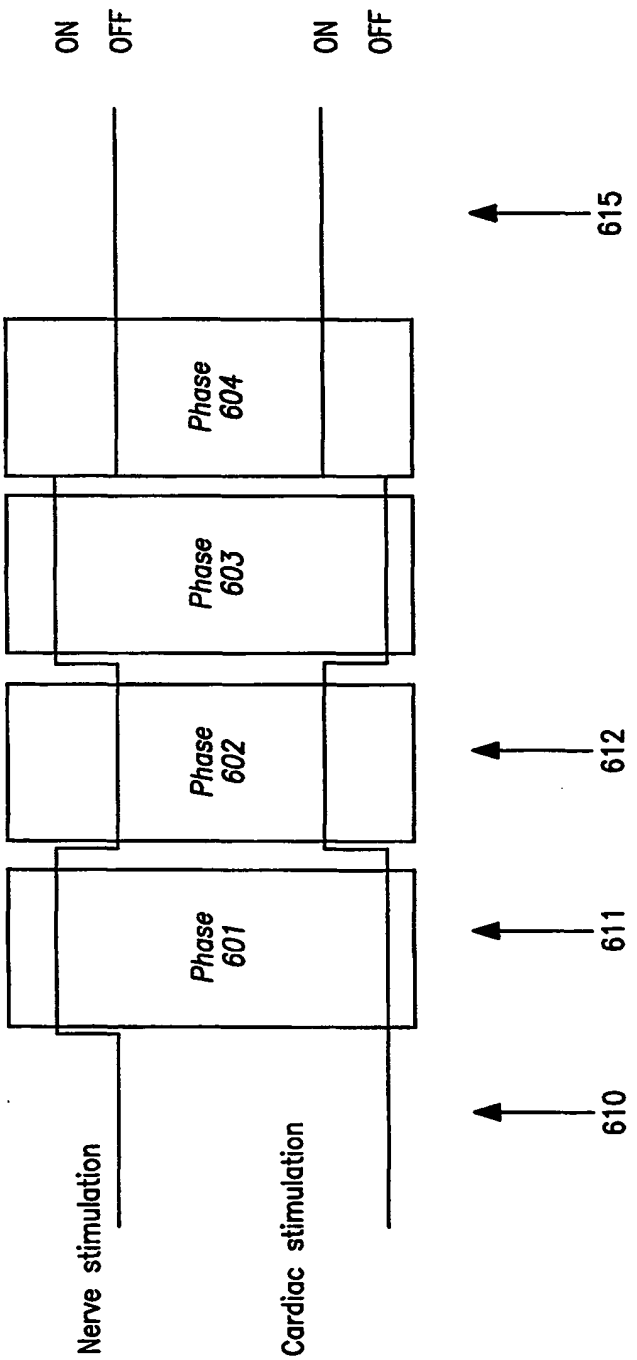
ON
OFF
ON
OFF
Phase 604
Phase 603
Phase 602
Phase 601
615
612
611
610
Nerve stimulation
Cardiac stimulation

FIG. 9

INTERNATIONAL SEARCH REPORT

ional Application No
PCT/US 01/30172

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/36 A61N1/362

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 63926 A (CPRX LLP) 16 December 1999 (1999-12-16) page 3, line 1 - line 33 page 15, line 29 -page 18, line 26 page 20, line 5 -page 21, line 18 figures	29-33,35
Y		34,36-42
Y	WO 00 09206 A (MEDTRONIC INC) 24 February 2000 (2000-02-24) page 2, line 24 -page 3, line 28	34,36-42
A	US 6 006 134 A (JONKMAN KENNETH R ET AL) 21 December 1999 (1999-12-21) cited in the application the whole document	29-34, 36-40

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2002	14/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ferrigno, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/30172

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			IL	74427 A	15-08-1989

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/30172

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 417 713 A (COHEN TODD J) 23 May 1995 (1995-05-23) the whole document	29-34, 36-40
A	US 5 913 876 A (MOREJOHN DWIGHT P ET AL) 22 June 1999 (1999-06-22) cited in the application the whole document	29-34, 36-40
A	US 4 574 807 A (HEWSON CARL ET AL) 11 March 1986 (1986-03-11) the whole document	29,36